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Estimated Phthalate Exposure and Risk to Pregnant Women and Women of Reproductive Age as Assessed Using Four NHANES Biomonitoring Data Sets (2005/2006, 2007/2008, 2009/2010, 2011/2012)

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Executive Summary

Section 108 of the Consumer Product Safety Improvement Act of 2008 ("CPSIA") required the Commission to convene a Chronic Hazard Advisory Panel ("CHAP") to examine the effects on children's health of all phthalates and phthalate alternatives used in children's toys and child care articles. Section 108(b)(3) further required the Commission to promulgate a final rule, pursuant to section 553 of the Administrative Procedure Act ("APA"), not later than 180 days after the Commission received the final CHAP report. The final rule was to:

(A) determine, based on such report, whether to continue in effect the prohibition under paragraph (1) [interim prohibitions for any children's toy that can be placed in a child's mouth or child care article that contains concentrations of more than 0.1 percent of diisononyl phthalate ("DINP"), diisodecyl phthalate ("DIDP"), or di-n-octyl phthalate ("DnOP")], in order to ensure a reasonable certainty of no harm to children, pregnant women, and other susceptible individuals with an adequate margin of safety; and

(B) evaluate the findings and recommendations of the CHAP and declare any children's product containing any phthalates to be a banned hazardous product under section 8 of the Consumer Product Safety Act (15 U.S.C. 2057), as the Commission determines necessary to protect the health of children.

In July 2014, the CHAP submitted a final report to the Commission. This report included an analysis of biomonitoring data and associated estimates of phthalate exposure and risk to various populations, including pregnant women, women of reproductive age, and infants. For their analysis the CHAP used biomonitoring data from the 2005/2006 National Health and Nutrition Examination Survey ("NHANES") cycle, which was the most recent data available at the time of the CHAP's analysis (CHAP 2014, p. 31). Additional NHANES data sets reflecting each survey individual's phthalate burden became available following the drafting of the CHAP report. These data, however, were not incorporated into the CHAP report.

Because the CHAP did not incorporate the individual-specific NHANES data later than 2006 in the CHAP's report, the Commission directed staff to evaluate the NHANES data cycles that became available following 2005/2006. To do this, Health Science and Epidemiology staff first applied the CHAP's methodology for analysis of NHANES biomonitoring data and then verified that they could duplicate the results presented in the CHAP report (using NHANES 2005/2006 data). The staff then determined which portions of the later NHANES sets (2007/2008, 2009/2010, 2011/2012) could be analyzed in a valid statistical manner using the CHAP's method, and then analyzed the appropriate NHANES data sets. This analysis included estimates of phthalate exposure, individual phthalate risk, and the cumulative risk (*i.e.*, hazard index) for

multiple phthalates. Staff reported the data as the median, 95th percentile, and 99th percentile and also estimated the distribution of risk estimates and variance estimates.

Overall, CPSC and CHAP estimations for daily intakes, hazard quotients, and hazard indices were similar when assessed using the NHANES 2005/2006 biomonitoring data. The numbers of pregnant women in the data sets after 2005/2006 were too small to generate statistical estimates for this subpopulation. Statistical estimates for women of reproductive age (15-45) indicated that daily intakes of phthalates have changed over time. Most notably, the daily intake of DEHP has decreased, while the daily intake of DINP has increased. When compared to the 2005/2006 data set, the hazard index has decreased in the more recent data sets (2009/2010, 2011/2012).

Table of Contents

Abbreviations

ADI	Acceptable daily intake
BBP	Butyl benzyl phthalate
CDC	Centers for Disease Control and Prevention (U.S.)
CHAP	Chronic Hazard Advisory Panel
CI	Confidence interval
CPSC	U.S. Consumer Product Safety Commission
CPSIA	Consumer Product Safety Improvement Act of 2008
DBP	Dibutyl phthalate
DIBP	Diisobutyl phthalate
DEHP	Di(2-ethylhexyl) phthalate
DI	Daily Intake
DINP	Diisononyl phthalate
DNOP	Di-*n*-octyl phthalate
FHSA	Federal Hazardous Substances Act
HI	Hazard Index
HQ	Hazard Quotient
Log_{10}	Logarithm to the base 10
MBP	Monobutyl phthalate
MBzP	Monobenzyl phthalate
MCPP	Mono-(3-carboxypropyl) phthalate
MEHHP	Mono-(2-ethyl-5-hydroxy-hexyl) phthalate
MEHP	Mono(2-ethylhexyl) phthalate
MEOHP	Mono-(2-ethyl-5-oxo-hexyl) phthalate
MEP	Monoethyl phthalate
MIBP	Monoisobutyl phthalate
MINP	Mono(isononyl) phthalate
MOE	Margin of Exposure
N/A	Not available or specified
NHANES	National Health and Nutrition Examination Survey
PEAA	Potency Estimates for Antiandrogenicity
P-value	Probability value
PW	Pregnant women
WORA	Women of reproductive age (15-45 years old; non-pregnant)

1. Introduction

1.1 Background

The Consumer Product Safety Improvement Act ("CPSIA") of 2008 was signed into law on August 14, 2008. Section 108 of the CPSIA established regulatory and other requirements for CPSC regarding phthalates.

- Section 108(a) permanently prohibited the manufacture for sale, offer for sale, distribution in commerce, or importation in the United States of any "children's toy or child care article" that contains concentrations of more than 0.1 percent of di(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), or butyl benzyl phthalate (BBP).
- Section 108(b)(1) prohibited on an interim basis (until the final rule is promulgated) the manufacture for sale, offer for sale, distribution in commerce, or importation in the United States of any "children's toy that can be placed in a child's mouth or child care article" that contains concentrations of more than 0.1 percent of diisononyl phthalate (DINP), diisodecyl phthalate (DIDP), or di-n-octyl phthalate (DNOP).
- Section 108(b)(2) directed the Commission to convene a CHAP "to study the effects on children's health of all phthalates and phthalate alternatives as used in children's toys and child care articles."
- Section 108(b)(3) of the Act requires the Commission to promulgate a final rule to: (A) determine, based on such a report, whether to continue in effect the prohibition under paragraph (1), in order to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety; and (B) evaluate the findings and recommendations of the CHAP and declare any children's product containing any phthalates to be a banned hazardous product under section 8 of the CPSA (15 U.S.C. 2057), as the Commission determines necessary to protect the health of children.

As directed, the Commission appointed a CHAP to fulfill the requirements of section 108(b)(2). The CHAP held its first meeting on April 14, 2010, and met in other public sessions and teleconferences until its last meeting on January 29, 2014. After concluding their analysis, the CHAP reported the results of those examinations to CPSC on July 18, 2014. The final CHAP report included "recommendations to the Commission regarding any phthalates (or combinations of phthalates) in addition to those identified in subsection (a) or phthalate alternatives that the panel determines should be declared banned hazardous substances."

Staff provided a briefing package to the Commission on November 25, 2014 as the first step toward meeting the requirements of section 108(b)(3) of the Act. In the briefing package, staff

presented the CHAP's recommendations on phthalates and phthalate alternatives and also staff's recommendations for a proposed rule. Staff briefed the Commission on December 5, 2014, and a decisional meeting was held on December 17, 2014. The Commission issued a notice of proposed rulemaking ("NPR") in the *Federal Register* on December 30, 2014. The comment period for the NPR was originally to expire on March 16, 2015, but the Commission voted to extend that period until April 15, 2015. A total of 99 comments were submitted (CPSC-2014-0033).

Consistent with the statutory directive, the CHAP's recommendations to the Commission were, in part, based on risk estimates from a cumulative assessment that considered exposures from selected phthalates. The CHAP used biomonitoring data (urinary metabolite levels) from the 2005/2006 NHANES, which is conducted by the Centers for Disease Control and Prevention ("CDC"). The 2005/2006 data set was the most recent data available at the time the CHAP performed its analysis (CHAP 2014, p. 35).

At the Commission briefing on December 5, 2014, the Commission Chairman directed the staff to evaluate the more recent NHANES data sets.

1.2 CPSC Staff's Approach to the NHANES Biomonitoring Analysis

Staff subdivided the project into four distinct phases to systematically replicate the CHAP analysis and report results for each data set.

- Phase 1 – Replicate the CHAP's methodology for calculating phthalate daily intakes and hazard indices.
- Phase 2 – Validate the methodology by using 2005/2006 NHANES data (*i.e.*, compare staff results to that of the CHAP)
- Phase 3 – Examine the more recent data sets to assess which subpopulations can be analyzed in a valid statistical manner using the CHAP's methodology. Specifically, determine whether there are sufficient numbers of pregnant women in the newer data sets to support the analysis.
- Phase 4 – Analyze the more recent data sets on specific target populations using the CHAP's methodology.

2. Phase 1 - Replication of the CHAP's Methodology for Estimating Exposure and Hazard Indices Using Factors Presented in the CHAP Report on Phthalates

The CHAP estimated cumulative exposure to phthalates quantitatively by using 2005/2006 NHANES biomonitoring data (*i.e.,* measurement of the phthalate metabolite in a person's urine) that was available at the time of their analysis (CPSC, 2014). Additional NHANES data sets have been released to the public after that analysis.

2.1 Biomonitoring Data Availability

Four NHANES biomonitoring data cycles are currently publicly available for use in calculating exposure to phthalates (2005/2006, 2007/2008, 2009/2010, 2011/2012). The most recent phthalate biomonitoring data set (2013/2014) is not publicly available at the time of writing this report.

2.1.1 NHANES 2005/2006 Data

The CHAP used NHANES phthalate biomonitoring data from the 2005/2006 cycle to estimate cumulative exposure. These phthalate data (PHTHTE_D 2005−2006) were originally posted online by CDC in February 2010, revised by CDC in January 2012, and updated again by CDC in February 2012. Additional data files used to calculate exposures (BMX_D 2005−2006, DEMO_D 2005−2006, ALB_CR_D 2005−2006, UCPREG_D 2005−2006) were originally posted online in November 2007. DEMO_D 2005−2006 (demographics) was subsequently updated in January and September 2009.

In response to the updates, the CHAP revised its analysis in July 2012. There have been no subsequent CDC revisions to the 2005/2006 phthalate data set since February 2012.

2.1.2 NHANES 2007/2008, 2009/2010, 2011/2012 Data

Three additional NHANES phthalate data sets have been publicly released since the CHAP performed their data analysis. First release of these data sets occurred in October 2010 (PHTHTE_E 2007−2008), September 2012 (PHTHTE_F 2009−2010), and November 2013 (PHTHTE_G 2011−2012), for each data set. The last update for the phthalate data sets (PHTHTE_G 2011−2012) was in October 2014, and for other data sets used in calculating exposure (*e.g.* DEMO_G 2011−2012), January 2015.

2.2 Individuals Represented in the NHANES Data Sets

The four NHANES phthalate data sets contain biomonitoring and measurement data from individuals ranging from 6 to 85 years of age. For the four data sets (2005/2006, 2007/2008, 2009/2010, and 2011/2012), the number of individuals (2515, 2543, 2688, and 2453, respectively), women (1266, 1282, 1323, and 1208, respectively), and non-pregnant women of reproductive age ("WORA") 15 to 45 years old (471, 473, 522, and 477, respectively), and with a daily phthalate intake of > 0.0 µg/kg-day, were roughly similar. The number of women with a daily phthalate intake of > 0.0 µg/kg-day, who were pregnant ("PW"), as determined by self-reporting or a positive lab pregnancy test, were much smaller, however, in data cycles after 2005/2006 (130, 20, 26, and 18, respectively).

2.3 Exposure and Cumulative Hazard Index Estimation

Staff estimated phthalate daily intakes, hazard quotients, and cumulative hazard indices using the data conventions and assumptions described in the CHAP report on phthalates (Appendix D).

2.3.1 Daily Intakes

Staff first estimated daily intakes ("DI"; µg/kg-day) for eight phthalates (BBP, DBP, DEHP, DEP, DMP, DIBP, DIDP, DINP) for each individual considering the following:

- If the measured phthalate metabolite was below the analytical limit of detection (LOD), the LOD/square root of 2 was used as the phthalate metabolite concentration.
- Creatinine excretion was estimated using formulas from Table 2. of Mage et al. (2008), heights and weights from NHANES BMX_ data files, and ages and races from NHANES DEMO_ data files. Creatinine excretion formulas used for non-Hispanic whites were also used for Mexican American, other Hispanic, and multiracial populations.
- Pregnancy status was determined by using the RIDEXPRG_ variable in the NHANES DEMO_ data file.
- Table D-1 of the CHAP report was used for parent phthalate molecular weight, phthalate metabolite molecular weight, and excretion factors (F_{ue}) for each phthalate metabolite.

2.3.2 Hazard Quotients

Staff then estimated hazard quotients ("HQ") for five anti-androgenic phthalates (DBP, BBP, DINP, DIBP, DEHP) for each individual, by dividing the daily intake by Potency Estimates for Antiandrogenicity ("PEAA") developed by the CHAP (Appendix D, section 4). The PEAA is an estimate of the level of exposure at which the risk of antiandrogenic effects is considered negligible. These three PEAAs were termed "Cases":

- Case 1 – published reference values for antiandrogenicity from a cumulative risk assessment for phthalates (Kortenkamp and Faust 2010),
- Case 2 – relative potency estimates derived by the CHAP based on comparisons across chemicals from the same study (Hannas et al. 2011b),
- Case 3 – *De novo* determination of reproductive and developmental reference values by the CHAP from information in the published literature.

2.3.3 Hazard Indices

Finally, the staff estimated hazard indices ("HI") for each individual by summing the HQs for the five anti-androgenic phthalates (DBP, BBP, DINP, DIBP, DEHP) for each PEAA Case.

3. Phase 2 - Validation of the Staff's Methodology by Comparison to Selected Results from the CHAP Report on Phthalates Using 2005/2006 NHANES Data

3.1 Analyzing NHANES Data Sets

As described, CPSC staff applied the same data conventions and methods used by the CHAP to estimate phthalate DIs and HQs/HIs for PW and WORA.

3.2 Reproduction of the CHAP's Results for NHANES 2005/2006

CPSC staff independently replicated the estimates from the CHAP report for phthalate exposures using the NHANES 2005/2006 data set, including DIs (Table 1 and 2), HQs, and HIs (Table 3). In most cases, median and 99th percentile estimates of phthalate DI were exactly as reported in Table D-2 of the CHAP report. Very minor differences in daily intakes were attributed to arithmetic rounding. Differences in DI did not substantially affect HI estimates, which were also similar to that presented in the CHAP report.

Table 1: CPSC Results Comparison to CHAP Daily Intake Estimates for Adults 15-45 Using NHANES 2005/2006 (CHAP Report Table D-2)

Daily Intake Estimates (µg/kg-day)	Phthalate (Adults 15-45)							
	BBP	DBP	DEHP	DEP	DMP	DIBP	DIDP	DINP
Median Estimate								
CHAP	0.29	0.66	3.8	3.3	0.03	0.19	1.5	1.1
CPSC	0.29	0.66	3.8	3.2	0.03	0.19	1.5	1.1
99th Percentile Estimate								
CHAP	2.5	5.5	203	118	0.80	1.9	19	35
CPSC	2.5	5.4	204	109	0.78	1.9	19	37

Table 2: CPSC Results Comparison to CHAP Daily Intake Estimates for Pregnant Women Using NHANES 2005/2006 (CHAP Report Table D-2)

Daily Intake Estimates (µg/kg-day)	Phthalate (Pregnant Women)							
	BBP	DBP	DEHP	DEP	DMP	DIBP	DIDP	DINP
Median Estimate								
CHAP	0.30	0.63	3.5	3.4	0.05	0.17	1.5	1.0
CPSC	0.28	0.63	3.5	3.3	0.05	0.17	1.5	1.0
99^{th} Percentile Estimate								
CHAP	2.7	6.4	366	357	0.68	2.0	11	27
CPSC	2.6	6.3	366	355	0.68	2.0	11	27

Table 3: CPSC Results Comparison to CHAP Hazard Index by PEAA Case for Pregnant Women Using NHANES 2005/2006 (CHAP Report Table D-9)

		Hazard Index Percentile Estimates (Pregnant Women)			
Estimated By	PEAA Case	Median	75^{th} Percentile	95^{th} Percentile	99^{th} Percentile
CHAP	Case 1	0.14	0.26	6.1	12.2
	Case 2	0.13	0.23	3.7	7.4
	Case 3	0.08	0.15	3.6	7.3
CPSC	Case 1	0.14	0.26	6.1	12.2
	Case 2	0.12	0.23	3.7	7.4
	Case 3	0.08	0.16	3.6	7.3

4. Phase 3 - Assess Which Subpopulations Can Be Appropriately Analyzed Using the CHAP's Methodology (Pregnant Women Versus Women of Reproductive Age)

Behaviorally, PW have increased consumption of fats, cheese, meat, and fruits and typically have a more health-conscious attitude when compared to non-pregnant women (Verbeke and De Bourdeaudhuij, 2007). Pregnant women also differ physiologically from non-pregnant WORA and have increased total blood volume (~30-45%), plasma volume (~40-60%), RBC volume (~25-33%), creatinine clearance (~21-41%), total plasma testosterone, and decreased metabolic clearance rate of testosterone (O'Leary et al., 1991; Picciano, 2003). The differences in these factors can result in differences in exposures to phthalates between these two populations.

Despite these differences, various publications suggest that daily phthalate or other chemical exposures are similar when comparing PW and WORA. Woodruff et al. (2011) determined that the geometric means and medians for many chemicals monitored in the NHANES 2003/2004 data set (including urinary MBzP, MIBP, MBP, and MEP) were similar for PW and WORA. Arbuckle et al. (2014) reported similar findings, in that uncorrected median concentrations of MBP, MBzP, MEHHP, MEHP, MEOHP, MCPP, and MEP in urine of PW in the MIREC study (2008−2011) were similar to WORA (20−39 yo) in a Canadian national health study (2007−2009, 2009−2011). The CHAP also concluded that the exposures to PW and WORA were not significantly different (CHAP, 2014; p36). So overall, in spite of the behavioral and physiological differences between WORA and PW, there is evidence to suggest that WORA have similar chemical exposures to PW.

4.1 Pregnant Women in NHANES 2007/2008, 2009/2010, and 2011/2012 Can Not Be Used for Statistical Estimates

There are an insufficient number of pregnant women in each of the NHANES cycles following NHANES 2005/2006 to generate statistically stable estimates for daily phthalate intakes. This is because, in subsequent cycles, NHANES no longer oversampled pregnant women, leaving the sample size of pregnant women too small to use for statistical analyses in those later cycles (NCHS 2012, NCHS 2013b).

In certain circumstances, NHANES data from different cycles can be combined to increase the number of individuals in the analysis. This is not the case with NHANES phthalate data, however. NHANES cycles 2005/2006, 2007/2008, 2009/2010, 2011/2012 cannot be combined to produce stable estimates related to phthalate DIs because all but dimethyl phthalate ("DMP") evidenced a statistical trend across time when analyzing subpopulations containing sufficient numbers of individuals. The detected trend in larger subpopulations for phthalates DIs cannot be

ruled out for the PW subpopulation; therefore, combining NHANES cycle data for PW was not attempted for any of the phthalates in this assessment (NCHS 2013c).

4.2 Women of Reproductive Age in NHANES 2005/2006, 2007/2008, 2009/2010, and 2011/2012 Can Be Used for Statistical Estimates

There are sufficient WORA (non-pregnant women ages 15 through 45) sampled after the 2005/06 NHANES cycle to generate stable statistical estimates for daily phthalate intakes for each cycle. As noted above, NHANES cycles 2005/2006, 2007/2008, 2009/2010, and 2011/2012 for any subpopulation, including WORA, were not combined because of the existence of trends in phthalate DI estimates; however, combining cycles was unnecessary to obtain stable estimates associated with phthalate exposure for WORA, in general (NCHS 2013c).

4.3 Phthalate Exposures for Pregnant Women Versus Women of Reproductive Age in NHANES 2005/2006

Staff compared their estimates from the 2005/2006 NHANES data set to determine whether WORA had similar DIs and HIs as PW. Median and 95th percentile estimates of the DIs for five phthalates were similar when comparing WORA to PW. The DIs were also similar to that in the CHAP report (CHAP, 2014; Table 2.7). Table 4 provides the median and 95th percentile estimates for daily intake estimates for five phthalates.

Table 4: Daily Intake Estimates (µg/kg-d): Comparison of Women of Reproductive Age Versus Pregnant Women Using NHANES 2005/2006

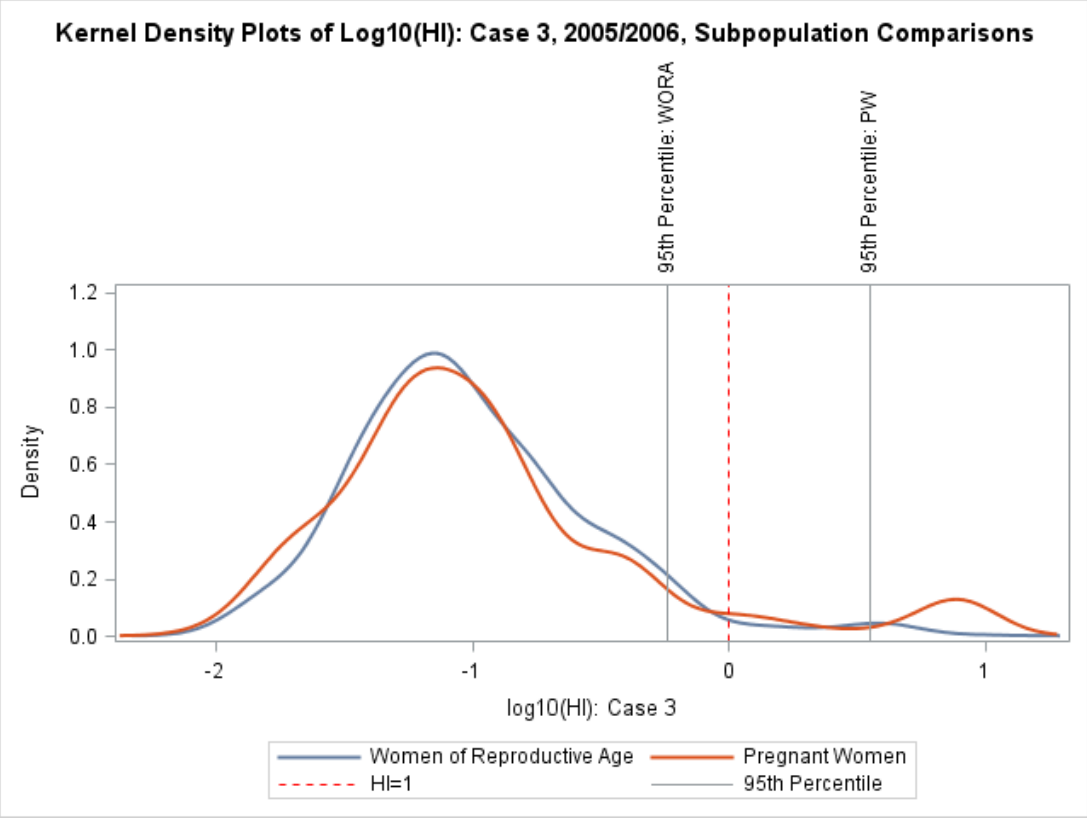
Subpopulation	BBP	DEHP	DINP	DBP	DIBP
Median					
WORA (CPSC, NHANES 2005/2006)	0.26	3.8	1.0	0.69	0.19
Pregnant Women (CPSC, NHANES 2005/2006)	0.28	3.5	1.0	0.63	0.17
95th Percentile*					
WORA (CPSC, NHANES 2005/2006)	1.1	27.7	10.5	2.6	0.82
Pregnant Women (CPSC, NHANES 2005/2006)	1.3	182	11.1	3.3	1.0

*Statistical test for comparisons cannot be performed on the 95th percentile estimates, because variance estimates are not always obtainable mathematically.

The median estimates of HIs for all three PEAA cases appeared similar for WORA and PW, although some differences existed in the upper tails of the empirical HI distributions. Figure 1 illustrates the empirical HI distribution comparisons for PW versus WORA using PEAA Case 3.

Statistical significance of any differences in the upper percentile estimates could not be assessed. This was because variance estimates were unobtainable due to the limited sample size of PW in the 2005/2006 NHANES data set.

Figure 1: NHANES 2005/2006 Women of Reproductive Age Versus Pregnant Women Hazard Index, PEAA Case 3, Empirical Distribution Comparison



5. Phase 4 – Statistical Analysis of Estimated Phthalate Exposure and Risk to Women of Reproductive Age Using 2005/2006, 2007/2008, 2009/2010, and 2011/2012 NHANES Biomonitoring Data Sets

5.1 Daily Intake Estimates for Women of Reproductive Age across the 2005/2006, 2007/2008, 2009/2010, and 2011/2012 NHANES Biomonitoring Data Sets

Daily Intake estimates for WORA in NHANES Cycles 2005/2006, 2007/2008, 2009/2010, 2011/2012 indicate that DIs have changed in a statistically significant manner across NHANES cycles (Table 5). For example, DINP DIs have increased, while DEHP DIs have decreased. The DIs for most other phthalates have remained fairly steady across NHANES cycle years. Only one phthalate (DMP), showed no evidence of a statistical trend across NHANES cycles (not shown). DMP is not anti-androgenic and was not used in hazard index calculations.

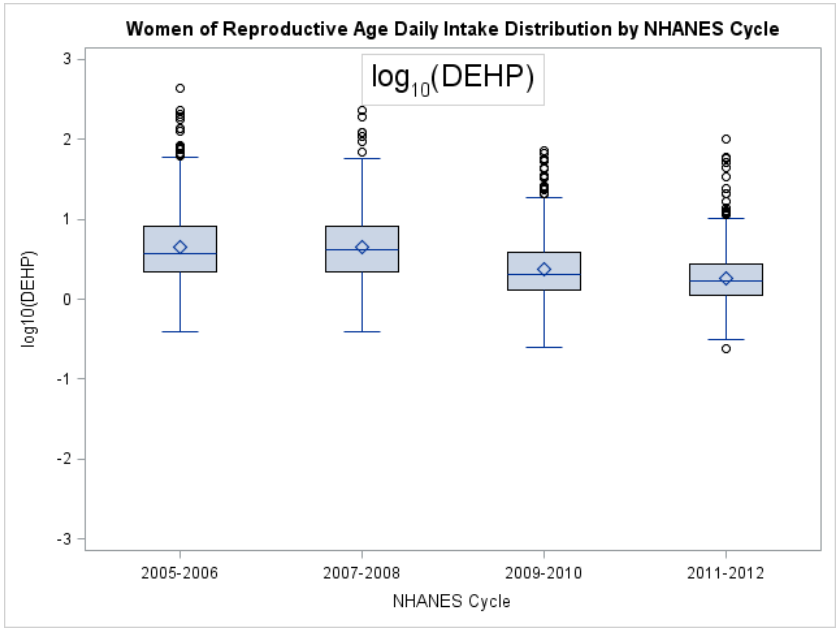
Table 5: Daily Intake Estimates (µg/kg-d) for Women of Reproductive Age Across NHANES Cycles: Median and 95th Percentile Estimates

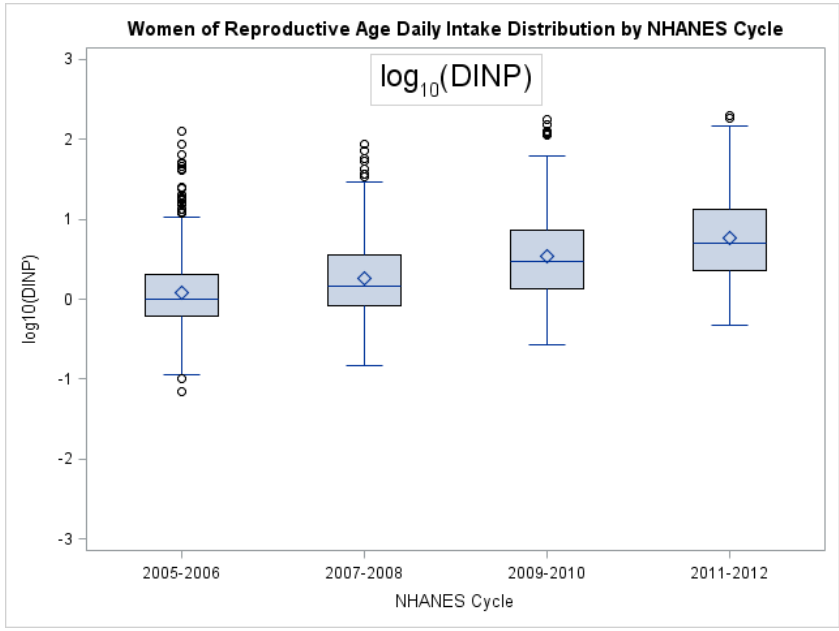
NHANES Data Set	BBP	DEHP	DINP	DBP	DIBP
Median					
NHANES 2005/2006	0.26	3.8	1.0	0.69	0.19
NHANES 2007/2008	0.29	4.1	1.5	0.79	0.29
NHANES 2009/2010	0.23	2.0	3.0	0.58	0.32
NHANES 2011/2012	0.19	1.7	5.0	0.33	0.26
95th Percentile					
NHANES 2005/2006	1.1	27.7	10.5	2.6	0.82*
NHANES 2007/2008	1.3	31.5	14.6	2.6	1.0
NHANES 2009/2010	1.0	10.3*	33.7	1.9*	0.98
NHANES 2011/2012	0.84	6.4*	51.7	1.3	0.94

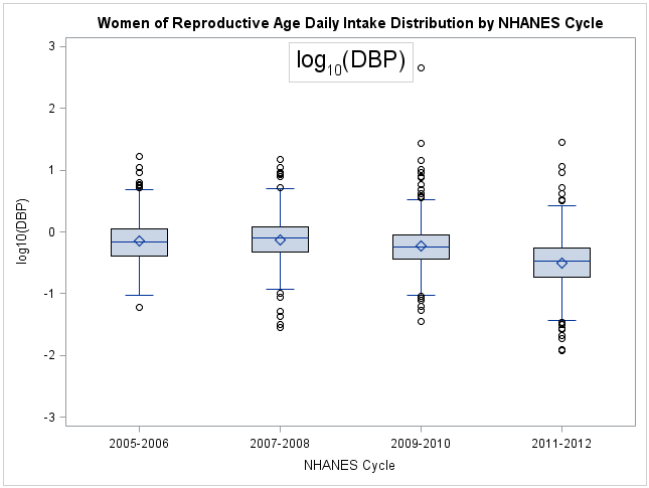
*Variance estimates can be large at the 95th percentile. Marked estimates are not considered stable. Use caution when drawing conclusions using 95th percentile estimates.

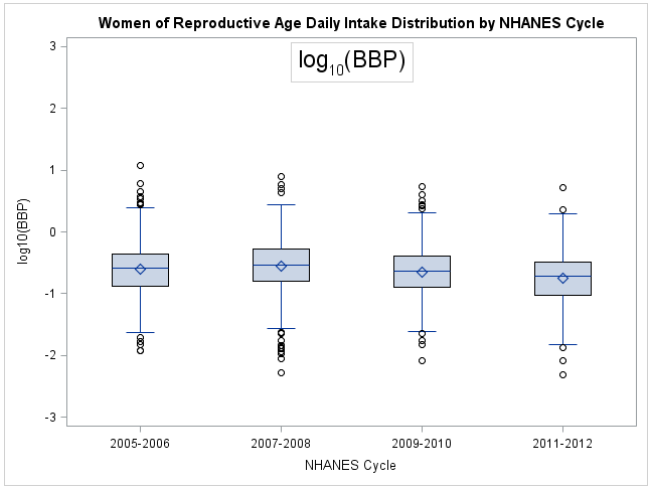
Figure 2 provides box-and-whisker plots of the empirical distributions of log_{10}-transformed daily intake distributions for five phthalates across NHANES cycles. There is a trend across cycles for each phthalate, including DINP and DEHP.

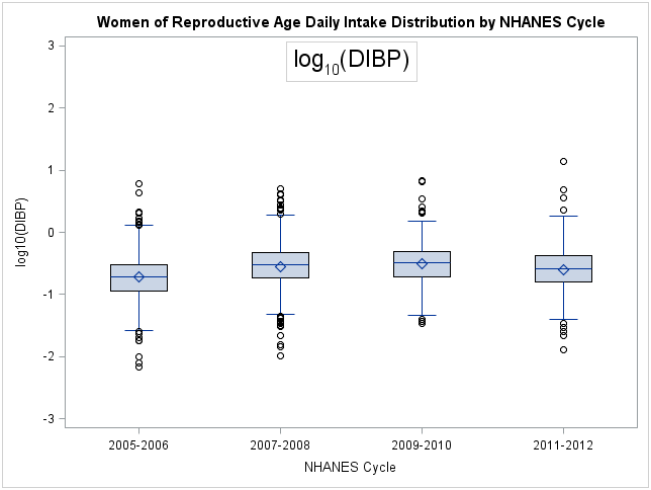
Figure 2: Log_{10}-Transformed Estimated Daily Intakes for 5 Phthalates for Women of Reproductive Age Across NHANES Cycles











5.2 Hazard Index Estimates for Women of Reproductive Age Across the 2005/2006, 2007/2008, 2009/2010, and 2011/2012 NHANES Biomonitoring Data Sets

Median, 95th percentile and 99th percentile, hazard index estimates decreased across the NHANES data cycles (Table 6 and Figures 3-5). The log_{10}-transformed HI values were fitted to cycle in a regression model to test for trends, and cycle-to-cycle comparisons were completed within the fitted model (see Appendix A). HI estimates for Cases 1 and 3 showed a significant downward trend from the 2005/2006 cycle to the 2011/2012 cycle ($p<0.001$). When comparing HIs from 2005/2006 to 2007/2008 within the regression model, no difference was detected for Cases 1, 2, and 3 ($p=0.91$, 0.41, 0.92, respectively). When comparing 2005/2006 to 2009/2010 within the model for Case 2, no difference was detected ($p=0.06$). For PEAA Case 2, however, even though the distributions of HI were roughly similar for each NHANES cycle, a trend could be detected statistically across all the data cycles ($p=0.016$).

Table 6: Hazard Index Estimates for Women of Reproductive Age Across NHANES Cycles: PEAA Case 1, 2, and 3

Percentile	PEAA Case	NHANES Cycle			
		2005/2006	2007/2008	2009/2010	2011/2012
Median	Case 1	0.14	0.15	0.09	0.07
	Case 2	0.13	0.15	0.12	0.11
	Case 3	0.08	0.09	0.06	0.05
95th Percentile	Case 1	0.95	1.1	0.43*	0.25
	Case 2	0.69*	0.77	0.60	0.60
	Case 3	0.58*	0.65	0.30*	0.24
99th Percentile**	Case 1	6.3	1.9	1.9	0.73
	Case 2	3.8	1.6	1.7	1.3
	Case 3	3.8	1.2	0.94	0.57

*Variance estimates can be large at the 95th percentile. Marked estimates are not considered stable.

**Variance estimates are not possible for the 99th percentile estimates or are very large. These estimates are not considered stable.

Figure 3: Kernel Density Plots for log_{10} Hazard Index for PEAA Case 1 by NHANES Cycle: Women of Reproductive Age

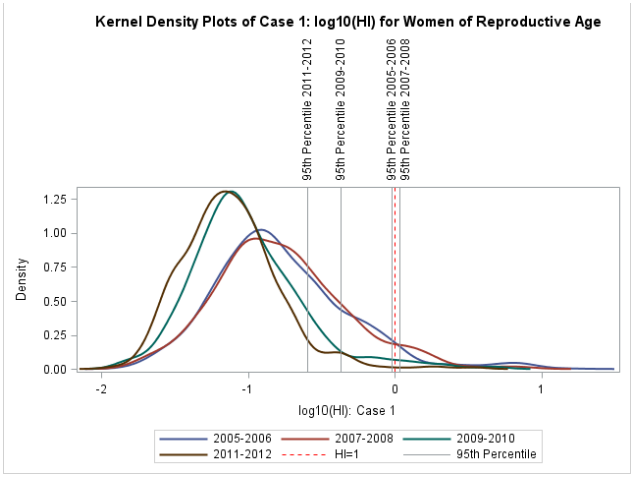


Figure 4: Kernel Density Plots for log_{10} Hazard Index for PEAA Case 2 by NHANES Cycle: Women of Reproductive Age

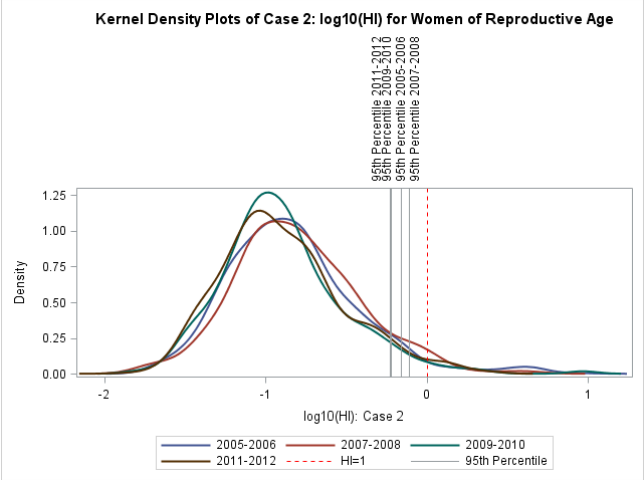
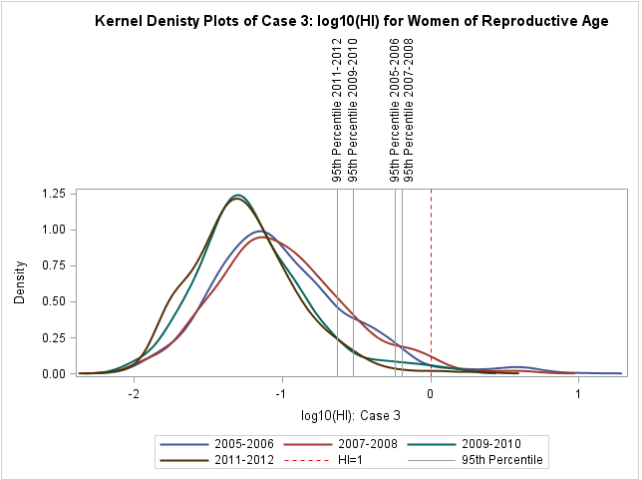


Figure 5: Kernel Density Plots for log_{10} Hazard Index for PEAA Case 3 by NHANES Cycle: Women of Reproductive Age



5.3 Percent of the Hazard Index that Phthalate Hazard Quotients Contribute

Figures 6 and 7 illustrate the impact that HQs have on the HI (sum of the HQs) across NHANES data cycles when looking at all PEAA Cases. In Figure 6, the sum of the median hazard quotients decreased in later data cycles (2009/2010, 2011/2012) when considering all PEAA Cases. As the HQ of DEHP decreased in later data cycles, the HQ of DINP increased. The contribution of DINP to the sum of the HQs (HI) depended on the PEAA Case. In PEAA Cases 1 and 3, DINP contributed a small portion to the sum of the HQs. In contrast, in PEAA Case 2, DINP contributed a large portion to the sum of the HQs, especially in later data sets (2009-2010, 2011-2012). Similar trends were repeated in Figure 7, which displayed the 95th percentile hazard quotients.

Figure 6: Median HQs for Women of Reproductive Age by NHANES Data Cycle and PEAA Case

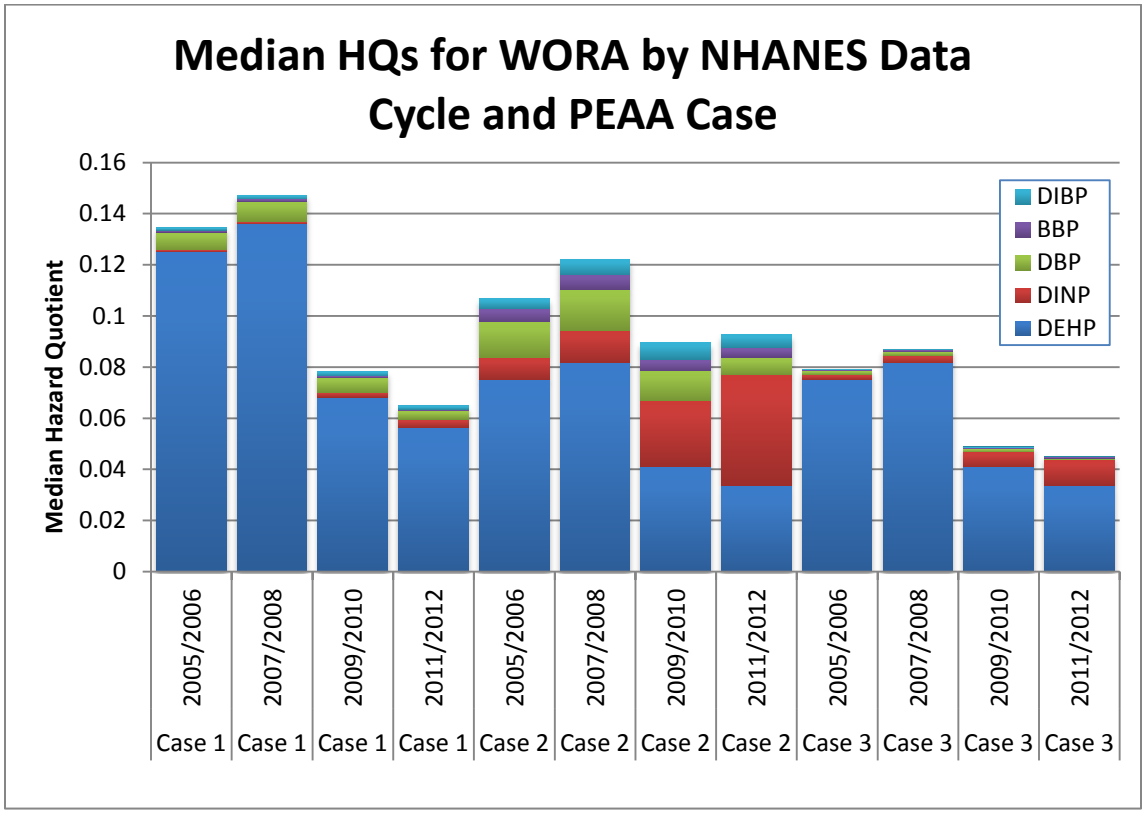
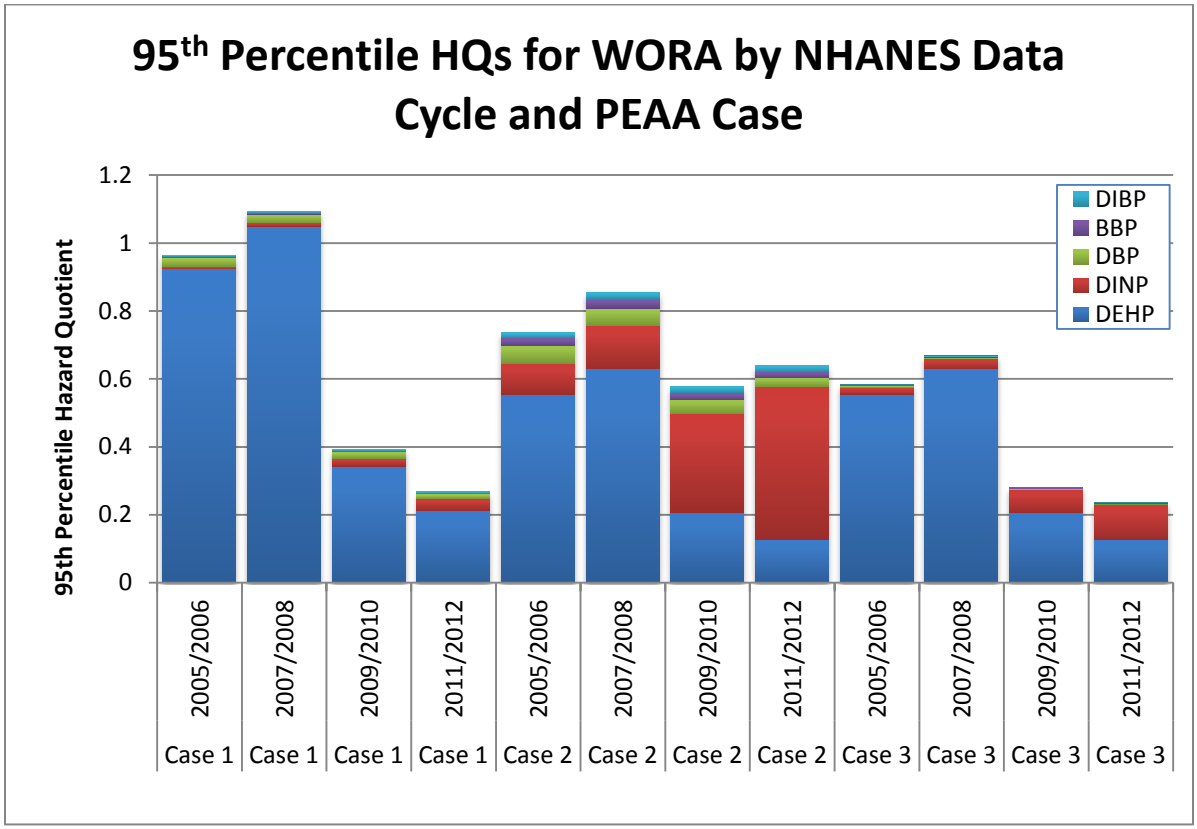


Figure 7: 95th Percentile HQs for Women of Reproductive Age by NHANES Data Cycle and PEAA Case



*95th percentile HQ estimates for DIBP in 2005/2006, DBP in 2009/2010, and DEHP in 2009/2010 have large variances. Estimates are not considered stable.

5.4 Estimated Proportion of Women of Reproductive Age with a Hazard Index >1 across the 2005/2006, 2007/2008, 2009/2010, and 2011/2012 NHANES Biomonitoring Data Sets

The estimated proportion of the WORA with a HI greater than one for each of the PEAA Cases decreases across the NHANES cycles (Table 7). In the 2011/2012 cycle year, <1 percent of WORA have an HI greater than one when considering PEAA Cases 1 and 3. For PEAA Case 2, an estimated 2.3 percent of WORA have a HI greater than one in the same cycle.

The estimated number of WORA represented by 1% of the subpopulation were obtained by summing the NHANES weights for the WORA phthalate samples.

Table 7: Estimated Percent of the Women of Reproductive Age Subpopulation with Hazard Index >1 by PEAA Case and NHANES Cycle

	NHANES Cycle			
PEAA Case	2005/2006	2007/2008	2009/2010	2011/2012
Case 1	4.2%	6.2%	2.6%*	<1%*
Case 2	3.1%	3.3%*	2.3%*	2.3%
Case 3	2.9%	1.9%*	<1%*	<1%*
1%=	540,000	586,000	576,000	602,000

*Marked estimates have a coefficient of variance that is considered high; these estimates are not considered stable.

5.5 Analytical Summary of the Results of Phthalate Exposure for Women of Reproductive Age Across the 2005/2006, 2007/2008, 2009/2010, and 2011/2012 NHANES Biomonitoring Data Sets

Median, 95th percentile, and 99th percentile HIs decrease over later NHANES data cycles. The percent of WORA with HIs greater than one decreases in later data cycles. The changes in HI distributions across NHANES cycles can be attributed to the changes in DEHP and DINP exposures. The decreases in HI are primarily due to decreases in DEHP. The HQ for DINP is replacing the HQ for DEHP proportionally for contributions to the total HI. In each PEAA Case, DINP has less potency than DEHP; thus even though DINP is taking DEHPs place in the proportion of contribution to total HI, the values of HI have still decreased overall across cycles.

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Appendix 1. Statistical Methodology

NHANES includes a health examination data survey that is nationally representative of the civilian, non-institutionalized U.S. Population. It is a complex, four-stage survey, which includes strata and primary sampling units ("PSUs") that must be accounted for when analyzing the data. The structure of NHANES also incorporates weights for each observation. Within NHANES, there are different subsamples of the total sample for different laboratory results, which are each weighted accordingly.

Staff used SAS 9.4® survey procedures to analyze the data. The strata, PSU, and lab subsample weight NHANES variables were incorporated per NHANES documentation. Domain analysis was incorporated to maintain the full structure of the survey in generating variance estimates for the various subsamples analyzed. Variance estimates were obtained using the Taylor Series method and Woodruff's method, as appropriate.

Staff used kernel density plots in place of histograms to assist in visual comparisons of distributions across subpopulation and NHANES cycles. Kernel density plots fit a non-parametric line to estimate the probability density function. Boxplots were used to visualize the distributions of phthalate daily intake estimated distributions. The log_{10} transformation was used on daily intakes and hazard index value to deal with the extreme skewness of the distribution of the raw values.

Staff set significance of p-values at an alpha of 0.05. Adjustments to p-values to account for multiple comparisons was not incorporated in the analysis (*i.e.*, p-values are provided in their original form). Trend across cycles was performed by linear regression while incorporating the survey's structure and applying domain analysis techniques. The p-values for trend correspond to the test for significance variable in a simple linear regression lines fitting the cycle as a classification variable for each log_{10}-transformed value of interest, individually. P-values for cycle-to-cycle comparisons were completed within the linear regression model. Though the log_{10}-transformed values did not always create models with all the model assumptions being met absolutely, the results indicated the model assumptions were met sufficiently to draw valid conclusions.